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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification⁶ : A61K 31/50, 31/505, 31/42	A1	(11) International Publication Number: WO 00/15229 (43) International Publication Date: 23 March 2000 (23.03.00)
(21) International Application Number: PCT/US99/20946 (22) International Filing Date: 13 September 1999 (13.09.99) (30) Priority Data: 60/100,677 17 September 1998 (17.09.98) US (71) Applicant: BRISTOL-MYERS SQUIBB COMPANY [-/US]; P.O. Box 4000, Princeton, NJ 08543-4000 (US). (72) Inventors: ROBL, Jeffrey, A.; 7 Tulip Drive, Newtown, PA 18940 (US). PARKER, Rex, A.; 147 Church Road, Titusville, NJ 08560 (US). BILLER, Scott, A.; 31 Second Street, Hopewell, NJ 08525 (US). JAMIL, Haris; 239 Burgundy Lane, Newton, PA 18940 (US). JACOBSON, Bruce, L.; 368 Vetterlein Avenue, Mercerville, NJ 08619 (US). KODUKULA, Krishna; 33 Douglass Drive, Princeton, NJ 08540 (US). (74) Agents: RODNEY, Burton et al.; Bristol-Myers Squibb Co., P.O. Box 4000, Princeton, NJ 08543-4000 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: METHOD FOR TREATING DIABETES EMPLOYING AN α P2 INHIBITOR AND COMBINATION (57) Abstract A method is provided for treating diabetes and related diseases, especially Type II diabetes, employing an α P2 inhibitor or a combination of an α P2 inhibitor and another antidiabetic agent such as metformin, glyburide, troglitazone and/or insulin.		

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METHOD FOR TREATING DIABETES EMPLOYING AN aP2
INHIBITOR AND COMBINATION

Field of the Invention

5 The present invention relates to a method for treating diabetes, especially Type II diabetes, as well as hyperglycemia, hyperinsulinemia, obesity, hypertriglyceridemia and related diseases, employing an aP2 inhibitor alone or in combination with another type
10 antidiabetic agent, and to the combination for use in such method.

Background of the Invention

15 Fatty acid binding proteins (FABPs) are small cytoplasmic proteins which bind to fatty acids such as oleic acids which are important metabolic fuels and cellular regulators. Dysregulation of fatty acid metabolism in adipose tissue is a prominent feature of insulin resistance and the transition from obesity to non-
20 insulin dependent diabetes mellitus (NIDDM or Type II diabetes).

 aP2, an abundant 14.6 KDa cytosolic protein in adipocytes, and one of a family of homologous intracellular fatty acid binding proteins (FABPs), is involved in the
25 regulation of fatty acid trafficking in adipocytes and mediates fatty acid fluxes in adipose tissue. G.S. Hotamisligil et al, "Uncoupling of Obesity from Insulin Resistance Through a Targeted Mutation in aP2, the Adipocyte Fatty Acid Binding Protein", Science, Vol. 274,
30 Nov. 22, 1996, pp. 1377-1379, report that aP2-deficient mice placed on a high fat diet for several weeks developed dietary obesity, but, unlike control-mice on a similar diet, did not develop insulin resistance or diabetes. Hotamisligil et al conclude that "aP2 is central to the
35 pathway that links obesity to insulin resistance" (Abstract, page 1377).

DIALOG ALERT DBDR928 dates January 2, 1997, Pharmaprojects No. 5149 (Knight-Ridder Information) discloses that a major drug company "is using virtual screening techniques to identify potential new antidiabetic compounds." It is reported that "the company is screening using aP2, a protein related to adipocyte fatty acid binding protein."

Description of the Invention

10 In accordance with the present invention, a method is provided for treating diabetes, especially Type II diabetes, and related diseases such as insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, obesity and hypertriglyceridemia
15 wherein a therapeutically effective amount of a drug which inhibits aP2 (aP2 inhibitor) is administered to a human patient in need of treatment.

In addition, in accordance with the present invention, a method is provided for treating diabetes and
20 related diseases as defined above and hereinafter, wherein a therapeutically effective amount of a combination of an aP2 inhibitor and another type antidiabetic agent is administered to a human patient in need of treatment.

Furthermore, in accordance with the present
25 invention, a novel antidiabetic combination is provided which is formed of a drug which inhibits aP2 and another type antidiabetic agent which functions by a mechanism other than by inhibiting aP2. The aP2 inhibitor will be employed in a weight ratio to the antidiabetic agent
30 (depending upon its mode of operation) within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 10:1.

The aP2 inhibitors suitable for use in the method of the invention are compounds which bind to the aP2 protein
35 and inhibits its function and/or its ability to bind free fatty acids. The compounds will preferably contain less than 60 carbon atoms, more preferably less than 45 carbon

atoms, and will contain less than 20 heteroatoms, more preferably less than 12 heteroatoms. They contain a hydrogen bond donator or acceptor group, preferably acidic in nature, which includes, but is not limited to, CO₂H, 5 tetrazole, SO₃H, PO₃H, P(R)(O)OH (where R is lower alkyl or lower alkoxy), OH, NHSO₂R' or CONHSO₂R' (where R' is lower alkyl), and thiazolidindione, and interacts (directly or through an intervening water molecule), either by ionic or hydrogen bonding interactions, with one, two, or three of 10 the three amino acid residues, designated as Arg 106, Arg 126 and Tyr 128 in human aP2, within the aP2 protein.

The compounds suitable for use herein preferably contain an additional substituent, preferably hydrophobic in nature, which include the following groups: alkyl, 15 cycloalkyl, aryl, heteroaryl, cycloheteroalkyl, benzo-fused aryl and heteroaryl, and their substituted counterparts. Especially preferred are aryl and substituted aryl groups. More especially preferred is phenyl and halo or methyl substituted phenyl.

20 The hydrophobic substituent binds to (in) and/or interacts with a discrete pocket within the aP2 protein defined roughly by the amino acid residues Phe 16, Tyr 19, Met 20, Val 23, Val 25, Ala 33, Phe 57, Thr 74, Ala 75, Asp 76, Arg 78 in human aP2. The through space distance from 25 the hydrogen bond donor/acceptor group and the additional substituent group is within the distance of about 7 to about 15 Angstroms.

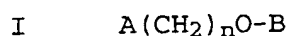
The above compounds may be employed in the form of pharmaceutically acceptable salts thereof and prodrug 30 esters thereof.

Brief Description of Figure

The accompanying Figure is a computer generated image of a partial X-ray structure of compound XVIA 35 (described hereinafter) bound to human aP2.

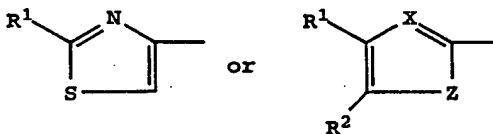
Detailed Description of the Invention

Examples of aP2 inhibitors suitable for use herein include compounds which include an oxazole or analogous ring. Thus, U.S. Patent No. 5,218,124 to Failli et al (the disclosure of which is incorporated herein by reference) discloses compounds, which have activity as aP2 inhibitors and thus suitable for use herein, which include substituted benzoylbenzene, biphenyl- and 2-oxazole-alkanoic acid derivatives having the following structure:



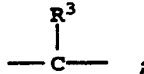
wherein

A is a group having the formula

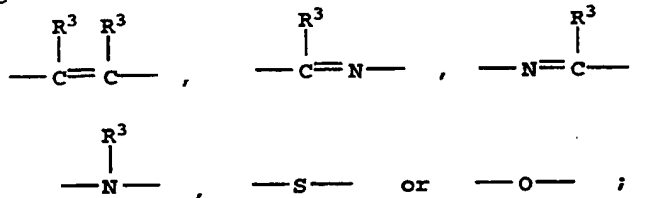


wherein

X is -N- or



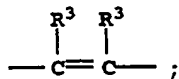
Z is



R^1 is hydrogen, lower alkyl or phenyl;

R^2 is hydrogen or lower alkyl; or

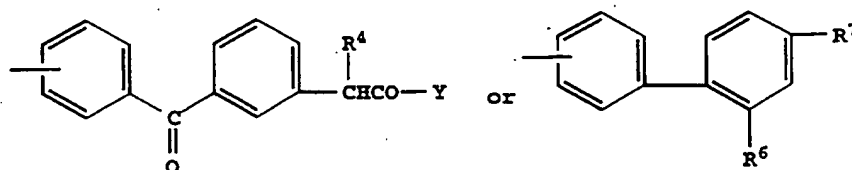
R^1 and R^2 taken together form a benzene ring, with the proviso that when X is -N-, Z is other than



R^3 is hydrogen or lower alkyl;

n is 1-2;

B is



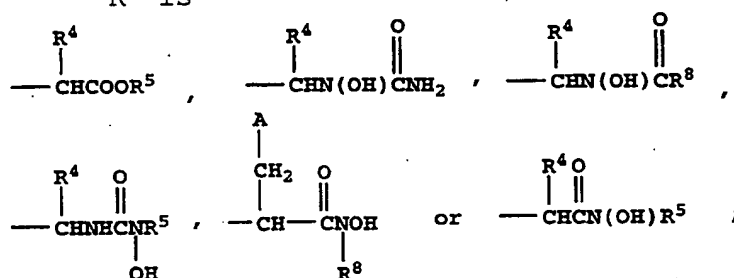
wherein

Y is OR⁵ or N(OH)R⁸;

R⁴ and R⁵ are each, independently, hydrogen or lower
5 alkyl;

R⁶ is hydrogen, halo or nitro;

R⁷ is



10 R⁸ is lower alkyl;

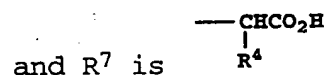
m is 0-3;

and the pharmacologically acceptable salts thereof.

The grouping A embraces, inter alia, 5- or 6-
15 membered unsaturated nitrogen, sulfur or oxygen containing
mono- or benzofused-heterocycles, optionally substituted
with lower alkyl or phenyl. The foregoing definition
embraces the following heterocyclic moieties; furyl,
pyrrolyl, thienyl, oxazolyl, thiazolyl, imidazolyl,
pyridyl, pyrazinyl, pyrimidinyl, benzofuranyl,
20 benzothienyl, benzothiazolyl, indolyl, benzoxazolyl,
quinazolinyl, benzimidazolyl, quinoxalinyl, quinazolinyl
and the like.

Preferred are the examples where A is defined as
above and B is

25

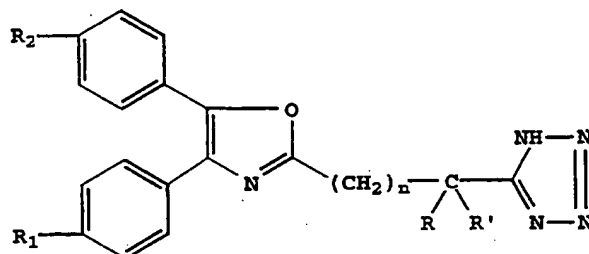


and R⁷ is

In another embodiment of the present invention,
compounds which have activity as aP2 inhibitors suitable

for use herein are disclosed in U.S. Patent No. 5,403,852 to Barreau et al (which is incorporated herein by reference) which are oxazole derivatives and have the structure

5 II



in which;

R and R' are identical or different and represent a hydrogen atom or an alkyl radical containing 1 or 2 carbon atoms,

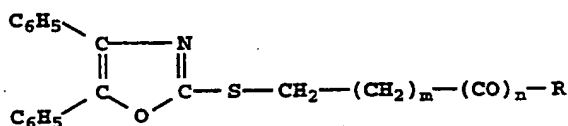
10 R₁ and R₂ are identical or different and represent hydrogen or halogen atoms or alkyloxy radicals in which the alkyl portion contains 1 to 4 carbon atoms in a straight or branched chain, and

15 n equals 3 to 6,

as well to their salts, to their isomers where they exist and to pharmaceutical compositions containing them.

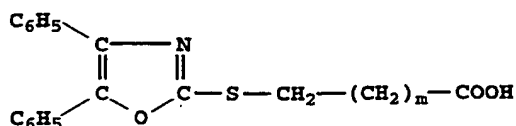
In addition, other compounds which have activity as aP2 inhibitors suitable for use in the method of the invention are compounds disclosed in U.S. Patent No. 4,001,228 to Mattalia (which is incorporated herein by reference) which are 2-thiol-4,5-diphenyloxazole S-derivatives which have the structure

25 III



wherein m is 0, 1 or 2, n is 1 and R represents hydroxy, alkoxy or amino. Also included within the scope of this invention are salts of the compounds of formula III above, particularly pharmaceutically acceptable addition salts thereof.

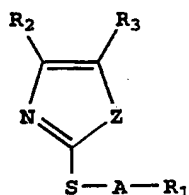
Preferred are S-(4,5-diphenyloxazol-2-yl)-mercaptocarboxylic acids of the formula:



5 wherein m is 0, 1 or 2, and pharmaceutically acceptable lower alkyl esters and salts thereof.

In another embodiment of the present invention, compounds which have activity as aP2 inhibitors suitable for use herein are disclosed in U.S. Patent No. 4,051,250
10 to Dahm et al (the disclosure of which is incorporated herein by reference) which discloses azole derivatives of the structure

IV

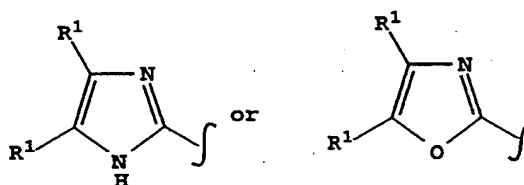
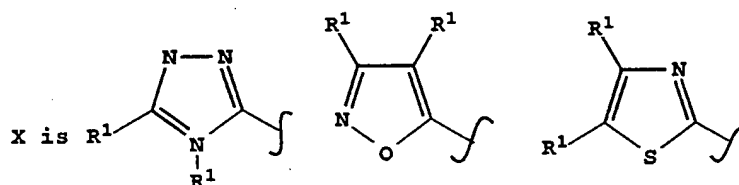
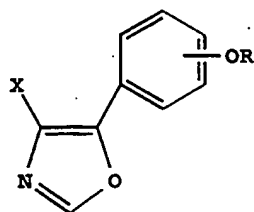
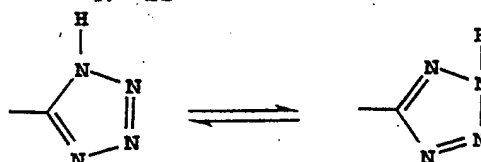


15 wherein R₁ is carboxyl, esterified carboxyl or other functionally modified carboxyl group; R₂ and R₃ each are aryl of up to 10 carbon atoms; A is C_nH_{2n} in which n is an integer from 1 to 10, inclusive; and Z is O or S, and the physiologically acceptable salts thereof.

20 Preferred are preferred compounds as disclosed in the Dahm et al patent.

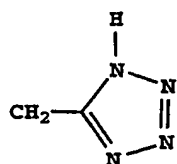
In still another embodiment of the invention, compounds which have activity as aP2 inhibitors suitable for use herein are disclosed in U.S. Patent No. 5,380,854 to
25 Romine et al (the disclosure of which is incorporated herein by reference) and are phenyl-heterocyclic oxazole derivatives which have the structure

V

R is CH_2R^2 ; R^1 is Ph or Th; R^2 is CO_2R^3 , and R^3 is H, or $\text{C}_1\text{-C}_4$ lower alkyl;

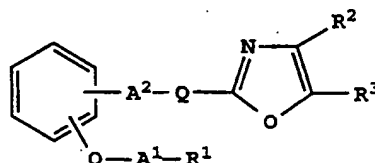
or pharmaceutically acceptable salt thereof.

10 Preferred are the compounds where R is $\text{CH}_2\text{CO}_2\text{H}$ and

or its tautomer and R^1 is Ph.

In yet another embodiment of the method of the invention, compounds which have activity as aP_2 inhibitors suitable for use herein are disclosed in PCT application WO
 15 95/17393 which are diaryloxazole derivatives having the structure

VI



wherein R¹ is carboxy or protected carboxy,

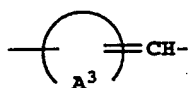
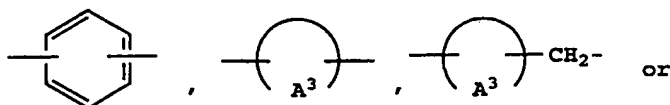
R² is aryl which may have suitable substituent(s),

5 R³ is aryl which may have suitable substituent(s),


A¹ is lower alkylene,

A² is bond or lower alkylene and

-Q- is



10

(in which  is cyclo (lower)alkane or cycle(lower)alkene, each of which may have suitable substituent(s)).

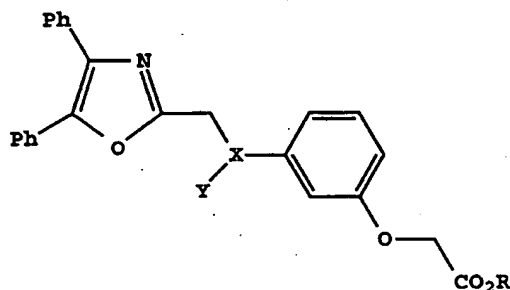
Preferred are the preferred compounds of WO 95/17393 as illustrated by the working Examples thereof.

15

Another embodiment of compounds which have activity as aP2 inhibitors suitable for use herein are disclosed in U.S. Patent No. 5,362,879 to Meanwell (the disclosure of which is incorporated herein by reference) which are 4,5-diphenyloxazole derivatives having the structures

20

VIIA

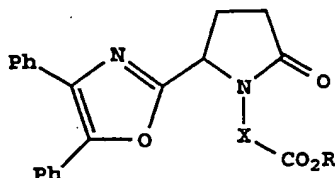


wherein

R is H or C₁-C₅ lower alkyl,

X is N or CH,
 Y is H or CO₂R¹, or COR²,
 R¹ is C₁-C₅ lower alkyl, or phenylmethyl, and
 R² is C₁-C₅ alkyl;

5 VIIB



wherein

R is H or C₁-C₅ lower alkyl,
 X is (CH₂)_n or para or meta substituted phenyl

10 wherein the substituent is OR²,

R² is C₁-C₅ alkyl, and

n is an integer of 4 to 8,

and pharmaceutically acceptable salts thereof.

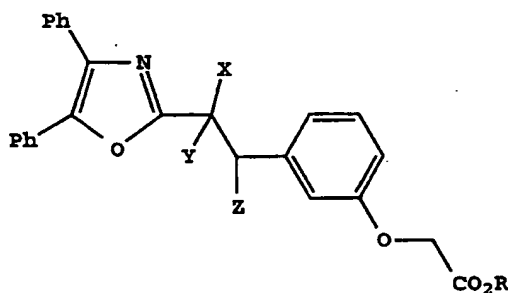
Preferred are the preferred compounds of the

15 Meanwell patent as illustrated by the working Examples thereof.

In still another embodiment of the present invention, compounds which have activity as aP2 inhibitors suitable for use herein are disclosed in U.S. Patent No.

20 5,187,188 to Meanwell (the disclosure of which is incorporated herein by reference) which are oxazole carboxylic acid derivatives having the structure

VIII



25 wherein

Y and Z are independently hydrogen or together form a bond;

X is CN, CO₂R¹ or CONR²R³;

R and R¹ are independently or together H, Na, or C₁-C₅ lower alkyl;

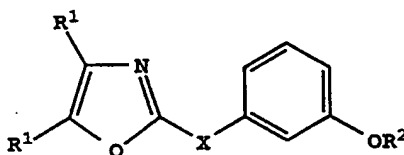
R² and R³ are independently or together H, or C₁-C₅ lower alkyl;

5 or alkali metal salt thereof.

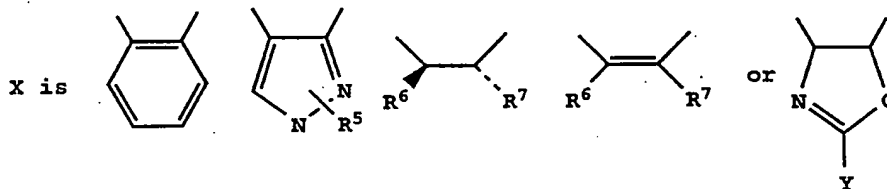
Preferred are the preferred compounds of the above Meanwell patent as illustrated by the working Examples thereof.

10 In another embodiment of the invention, compounds which have activity as aP2 inhibitors suitable for use herein are disclosed in U.S. Patent No. 5,348,969 to Romine et al (the disclosure of which is incorporated herein by reference) which are phenyloxazolyloxazole derivatives having the structure

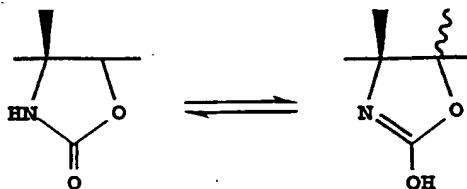
15 IX



wherein



Y is CH₃, Ph, or OH, provided that when Y is OH, the
20 compound exists in the keto-enol tautomerism form



R¹ is Ph or Th;

R² is CH₂R³;

R³ is CO₂R⁴;

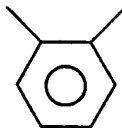
25 R⁴ is H or C₁-C₅ lower alkyl;

R⁵ is H or CH₃; R⁶ is OHCHN or H₂N; and

R⁷ is H or OH;

or pharmaceutically acceptable salt thereof.

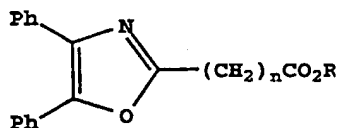
Preferred are the preferred compounds as delineated in the Romine et al patent and in the working Examples thereof, especially where X is



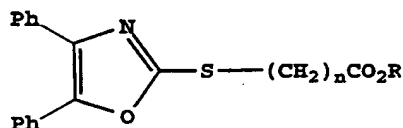
5 and R² is CH₂CO₂H.

In addition, compounds which have activity as aP2 inhibitors which may be employed herein include those disclosed in U.S. Patent No. 5,262,540 to Meanwell (the disclosure of which is incorporated herein by reference) and are 2-(4,5-diaryl)-2-oxazolyl substituted phenoxyalkanoic acids and esters having the structure

XA



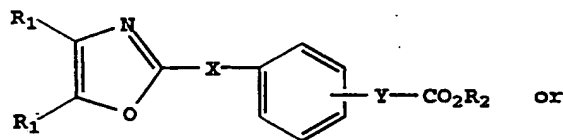
XB



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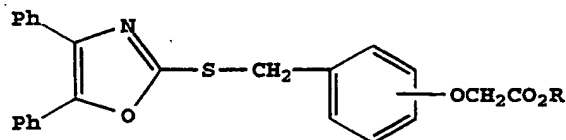
(wherein n is 7-9 and R is hydrogen or lower alkyl; or when R is hydrogen, the alkali metal salt thereof),

XC



20

XD



wherein

R₁ is phenyl or thienyl;

25 R₂ is hydrogen, lower alkyl or together with CO₂ is tetrazol-1-yl;

X is a divalent connecting group selected from the group consisting of CH_2CH_2 , $\text{CH}=\text{CH}$, and CH_2O ;

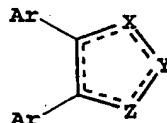
Y is a divalent connecting group attached to the 3- or 4-phenyl position selected from the group consisting of OCH_2 , CH_2CH_2 and $\text{CH}=\text{CH}$,

or when R_2 is hydrogen, an alkali metal salt thereof.

Preferred are the preferred compounds as set out in the above Meanwell et al patent as illustrated in the working Examples thereof.

In another embodiment of the invention, compounds which have activity as aP2 inhibitors suitable for use herein are disclosed in PCT application WO 92/04334 which are substituted 4,5-diaryl heterocycles having the formula

XI



in which

each group Ar is the same or different and is optionally substituted phenyl or optionally substituted heteroaryl;

X is nitrogen or CR^1 ;

Y is nitrogen, $\text{N}(\text{CH}_2)_n\text{A}$ or $\text{C}(\text{CH}_2)_n\text{A}$;

Z is nitrogen, oxygen or $\text{N}(\text{CH}_2)_n\text{A}$, and the dotted line indicates the optional presence of a double bond so as to form a fully unsaturated heterocyclic ring;

R^1 is hydrogen, C_{1-4} alkyl, optionally substituted phenyl or optionally substituted heteroaryl;

n is 4 to 12; and

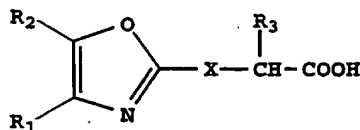
A is CO_2H or a group hydrolysable to CO_2H , 5-tetrazolyl, SO_3H , $\text{P}(\text{O})(\text{OR})_2$, $\text{P}(\text{O})(\text{OH})_2$, or $\text{P}(\text{O})(\text{R})(\text{OR})$ in which R is hydrogen or C_{1-4} alkyl, or a pharmaceutically acceptable salt thereof.

Preferred are preferred compounds of WO 92/04334.

In yet another embodiment of the invention, compounds which have activity as aP2 inhibitors suitable

for use herein are disclosed in French Patent 2156486 which have the structure

XII



5 Where X is O or S;

R₁ is H, phenyl or phenyl substituted with F, Cl or Br or alkoxy,

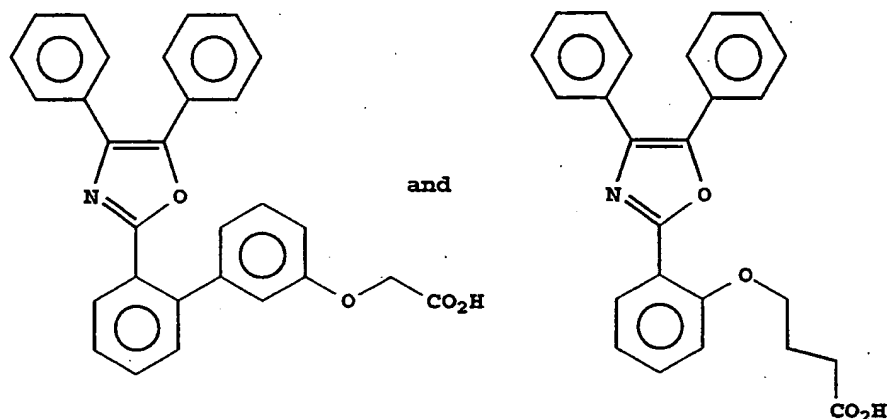
R₂ is H, alkyl, phenyl or phenyl substituted with F, Cl or Br or alkoxy, and

10 R₃ is H or alkyl.

Preferred are those preferred compounds as set out in French Patent No. 2156486.

Most preferred oxazole compounds as aP2 inhibitors are the compounds

15



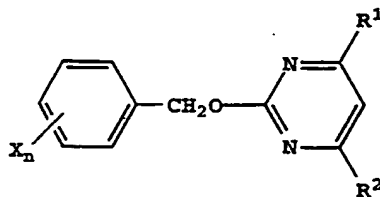
which may be prepared as disclosed in U.S. Patent No. 5,348,969 to Romine et al.

Another class of aP2 inhibitors suitable for use in the method of the invention include pyrimidine derivatives. Thus, U.S. Patent No. 5,599,770 to Kubota et al (the disclosure of which is incorporated herein by reference) disclose compounds which have activity as aP2 inhibitors and thus suitable for use herein include 2-benzoyloxypyrimidine derivatives having the following structure

20

25

XIII



wherein

R^1 and R^2 are each independently H, a halogen,
 5 hydroxyl, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_3 - C_5 alkenyl, C_3 - C_5
 alkynyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, C_3 - C_5 alkenyloxy,
 C_3 - C_5 alkynyloxy, C_1 - C_4 alkylthio, or phenyl, with the
 proviso that at least one of R^1 and R^2 must be hydroxyl;

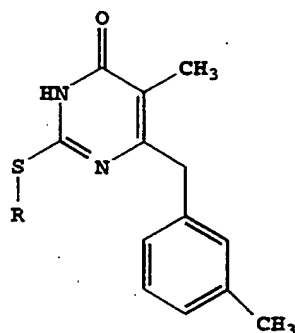
n is an integer of 0 to 5; and

10 each X which may be identical or different if n is
 greater than 1, is a halogen, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl,
 C_1 - C_4 alkoxy, C_1 - C_4 alkylthio, C_7 - C_9 aralkyloxy, phenyl,
 hydroxymethyl, hydroxycarbonyl, C_1 - C_4 alkoxy carbonyl, or
 nitro.

15 Preferred are the compounds in which either R^1 or R^2
 is hydroxyl and the other R^1 or R^2 is C_1 - C_4 alkyl and X is
 halogen.

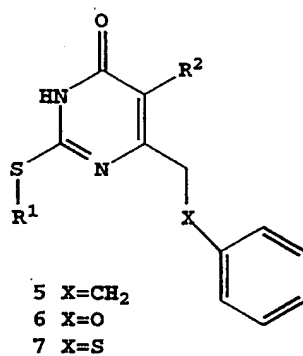
In another embodiment of the method of the
 invention, compounds which have activity as $aP2$ inhibitors
 20 suitable for use herein are disclosed in A. Mai et al
 "Dihydro(alkylthio)-(naphthylmethyl)oxypyrimidines: Novel
 Non-Nucleoside Reverse Transcriptase Inhibitors of the S-
 DABO Series", J. Med. Chem., 1997, 40, 1447-1454 which have
 the structures

XIVA



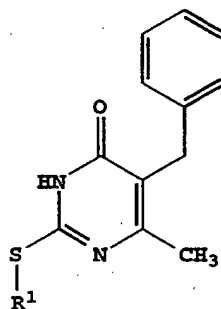
3a R=sec-butyl
 3b R=cyclopentyl
 3c R=cyclohexyl

XIVB

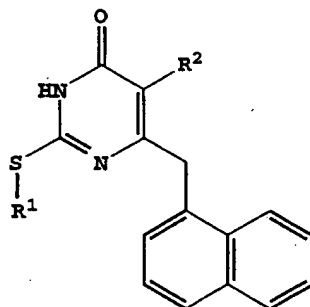


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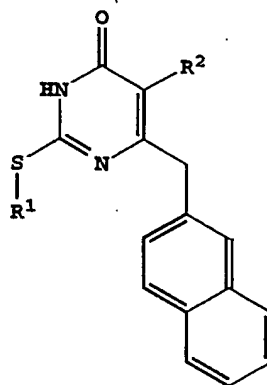
XIVC



XIVD



XIVE

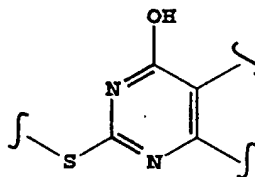


R^1 = sec-butyl, cyclopentyl, cyclohexyl;

R^2 = H, CH_3 . The structures XIVA-XIVE are depicted in

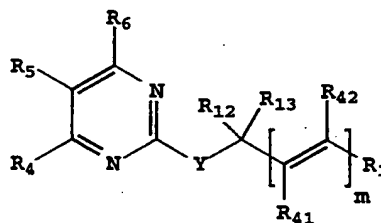
5 their keto form. However, it will be apparent to one skilled in the art that they may also exist in their enol form to give structures of the type

XIVF



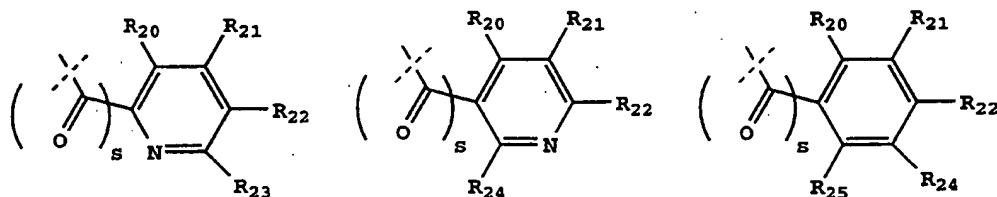
10 In yet another embodiment of the method of the invention, compounds which have activity as $\alpha P2$ inhibitors suitable for use herein are disclosed in PCT application WO 96/35678 which are α -substituted pyrimidine-thioalkyl and alkylether compounds which have the structure

15 XVI



where m is 0 or 1;

R^1 is selected from $-CO_2R_{53}$, $-CONR_{54}R_{55}$,



- where s is 0 or 1, and R_{20} , R_{21} , R_{22} , R_{23} , R_{24} , and R_{25} are the same or different and are selected from -H, C_1 - C_6 alkyl, C_1 - C_6 alkenyl, C_1 - C_6 alkoxy, C_1 - C_6 alkylthio, C_3 - C_8 cycloalkyl, $-CF_3$, $-NO_2$, -halo, -OH, -CN, phenyl, phenylthio, -styryl, $-CO_2(R_{31})$, $-CON(R_{31})(R_{32})$, $-CO(R_{31})$, $-(CH_2)_n-N(R_{31})(R_{32})$, $-C(OH)(R_{31})(R_{33})$, $-(CH_2)_nN(R_{31})(CO(R_{33}))$, $(CH_2)_nN(R_{31})(SO_2(R_{33}))$, or where R_{20} and R_{21} , or R_{21} and R_{22} , or R_{22} and R_{23} are taken together to form a five or six-
- 10 membered saturated or unsaturated ring containing 0 or 1 oxygen, nitrogen or sulfur, where the unsaturated ring may be optionally substituted with 1, 2 or 3, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, -OH, $-CH_2OH$, $-(CH_2)_n-N(R_{31})(R_{32})$, $-C_3$ - C_8 cycloalkyl, $-CF_3$, -halo, $CO_2(R_{31})$, $-CON(R_{31})(R_{32})$, $-CO(R_{31})$, $-(CH_2)_nN(R_{31})(CO(R_{33}))$, $-(CH_2)_nN(R_{31})(SO_2(R_{33}))$, -CN, $-CH_2CF_3$ or $-CH(CF_3)_2$, or phenyl and the saturated ring may be optionally substituted with 1, 2 or 3, $-C_1$ - C_6 alkyl, $-C_1$ - C_6 alkoxy, -OH, $-CH_2OH$ or $-(CH_2)_n-N(R_{31})(R_{32})$ or one oxo ($=O$);
- 15 where n is 0-3 and R_{31} , R_{32} and R_{33} are the same or different and are selected from
- 20 -H,
 C_1 - C_6 alkyl,
 phenyl optionally substituted with 1, 2 or 3 -halo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, $-CF_3$, -OH or -CN,
- 25 or where R_{31} and R_{32} taken together with the attached nitrogen to form a ring selected from -pyrrolidinyl, -piperidinyl, -4-morpholinyl, -4-thiomorpholinyl, -4-piperazinyl, -4-(1- C_1 - C_6 alkyl)piperazinyl, or a member selected from:
- 30 1-cyclohexenyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-imidazolyl, 4-imidazolyl, 2-benzothiazolyl, 2-benzoxazolyl, 2-benzimidazolyl, 2-oxazolyl, 4-oxazolyl, 2-thiazolyl, 3-isoxazolyl, 5-isoxazolyl, 5-methyl-3-

isoxazolyl, 5-phenyl-3-isoxazolyl, 4-thiazolyl, 3-methyl-2-pyrazinyl, 5-methyl-2-pyrazinyl, 6-methyl-2-pyrazinyl, 5-chloro-2-thienyl, 3-furyl, benzofuran-2-yl, benzothien-2-yl, 2H-1-benzopyran-3-yl, 2,3-dihydrobenzopyran-5-yl, 1-methylimidazol-2-yl, quinoxalin-2-yl, piperon-5-yl, 4,7-dichlorobenzoxazol-2-yl, 4,6-dimethylpyrimidin-2-yl, 4-methylpyrimidin-2-yl, 2,4-dimethylpyrimidin-6-yl, 2-methylpyrimidin-4-yl, 4-methylpyrimidin-6-yl, 6-chloropiperon-5-yl, 5-chloroimidazol[1,2-a]pyridin-2-yl, 1-H-inden-3-yl, 1-H-2-methyl-inden-2-yl, 3,4-dihydronaphth-1-yl, S-4-isopropenylcyclohexen-1-yl or 4-dihydronaphth-2-yl;

where R_{53} is selected from -H, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, phenyl (optionally substituted with 1, 2, or 3 -halo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, $-CF_3$, -OH, -CN), or a five or six-membered unsaturated ring containing 0 or 1 oxygen, nitrogen or sulfur, where the unsaturated ring may be optionally substituted with -H, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, -OH, $-CH_2OH$, or $-(CH_2)_n-N(R_{31})(R_{32})$;

where R_{54} and R_{55} being the same or different are selected from -H, C_1 - C_6 alkyl, allyl, or phenyl (optionally substituted with 1, 2 or 3 -halo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy or $-CF_3$), or taken together with the attached nitrogen to form a ring selected from -pyrrolidinyl, -piperidinyl, -4-morpholinyl, -4-thiomorpholinyl, -4-piperazinyl, -4-(1- C_1 - C_6 alkyl)piperazinyl;

R_{41} and R_{42} , being the same or different, are selected from -H and C_1 - C_4 alkyl;

R_{12} is selected from -H, C_1 - C_6 alkyl, $-C_3$ - C_6 cycloalkyl, -CN, $-C(O)NH_2$, $-C(O)N(C_1-C_6alkyl)(C_1-C_6alkyl)$, $-CO_2H$, $-CO_2(C_1-C_6alkyl)$, $-CH_2OH$, $-CH_2NH_2$ or $-CF_3$;

R_{13} is selected from -H, C_1 - C_6 alkyl or $-CF_3$;

Y is selected from -S-, $-S(O)-$, $-S(O)_2$, or -O-;

R_4 is -OH;

R_5 is selected from -H, $-C_2H_4OH$, $-C_2H_4-O-TBDMS$, halo, $-C_3$ - C_6 cycloalkyl, C_1 - C_3 alkoxy, $-CH_2CH_2Cl$ or C_1 - C_4 alkyl, with the proviso that R_5 is not isobutyl;

or, when R_6 is hydroxyl, R_4 and R_5 are taken together to form a five or six-membered saturated or unsaturated ring which together with the pyrimidine ring form the group consisting of 7H-pyrrolo[2,3-d]pyrimidine, 5,6-dihydro-7H-pyrrolo[2,3-d]pyrimidine, furo[2,3-d]pyrimidine, 5,6-dihydro-furo[2,3-d]pyrimidine, thieno[2,3-d]pyrimidine, 5,6-dihydro-thieno[2,3-d]pyrimidine, 1H-pyrazolo[3,4-d]pyrimidine, 1H-purine, pyrimido[4,5-d]pyrimidine, pteridine, pyrido[2,3-d]pyrimidine, or quinazoline, where the unsaturated ring may be optionally substituted with 1, 2 or 3, C_1 - C_6 alkyl C_1 - C_6 alkoxy, -OH, -CH₂OH, or -(CH₂)_n-N(R_{31})(R_{32}), - C_3 - C_8 cycloalkyl, -CF₃, -halo, -CO₂(R_{31}), -CON(R_{31})(R_{32}), -CO(R_{31}), -(CH₂)_nN(R_{31})(CO(R_{33})), -(CH₂)_nN(R_{31})(SO₂(R_{33})), and the saturated ring may be optionally substituted with 1, 2 or 3, - C_1 - C_6 alkyl, C_1 - C_6 alkoxy, -OH, -CH₂OH, or -(CH₂)_n-N(R_{31})(R_{32}) or one oxo (=O); and

R_6 is selected from -H, -OH, halo, -CN, -CF₃, -CO₂(R_{61}), -C(O) R_{61} or -C(O)N(R_{61})(R_{62}) where R_{61} and R_{62} are the same or different and are selected from

-H,

C_1 - C_6 alkyl,

phenyl optionally substituted with 1, 2 or 3 -halo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, -CF₃, -OH, -CN,

or where R_{61} and R_{62} taken together with the attached nitrogen to form a ring selected from -pyrrolidinyl, -piperidinyl, -4-morpholinyl, -4-thiomorpholinyl, -4-piperazinyl, or -4-(C_1 - C_6 alkyl)piperazinyl; or

pharmaceutically acceptable salts, hydrates, N-oxides and solvates thereof.

A preferred embodiment is pyrimidine-thioalkyl and alkylether, where

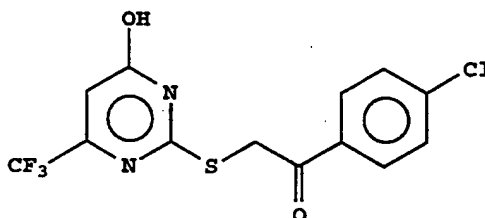
R_4 is -OH; and

R_6 is selected from -H, halo, -CN, -CF₃, -CO₂(R_{16}), -C(O) R_{61} or -C(O)N(R_{61})(R_{62}), preferably CF₃.

A preferred embodiment are compounds of Formula XVI where s is 0 or 1, and Y is -S- or -O-; more preferably Y is -S-.

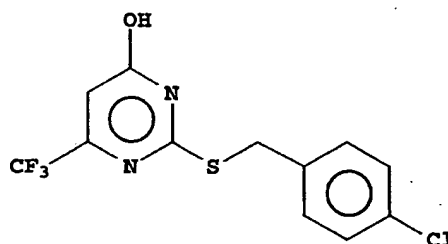
Preferred are pyrimidine derivatives of the structures

XVIA



and

XVIB



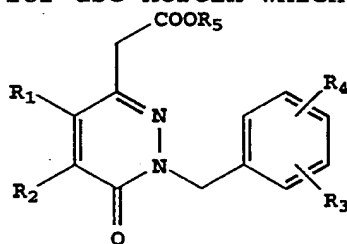
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which may be prepared as disclosed in WO 96/35678.

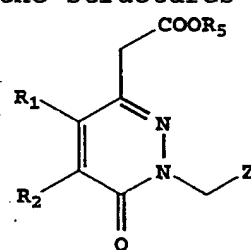
Another embodiment of the method of the invention includes use of aP2 inhibitors which are pyridazinone derivatives. French Patent No. 2,647,676 discloses compounds which have activity as aP2 inhibitors and thus

15

suitable for use herein which have the structures



XVIIA



XVIIIB

where R₁ and R₂ are H, alkyl, aryl or arylalkyl, where the alkyl can include as substituents halogen, CF₃, CH₃O, CH₃S, NO₂, or R₁ and R₂ with the carbons to which they are attached can form methylenedioxy, or

20

R₁ and R₂ can form a C₃-C₇ non-aromatic ring, or a heterocycle which can be pyridine, pyrazine, pyrimidine,

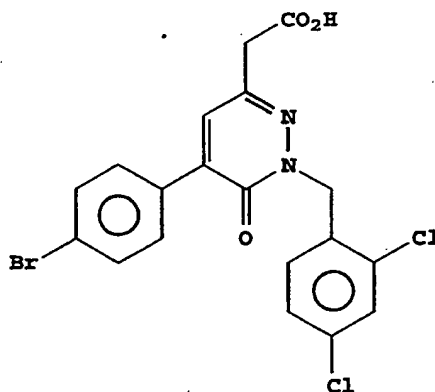
pyridazine, indol, or pyrazole, or an oxygen containing heterocycle which can be pyran or furan, or a sulfur containing heterocycle which can be thiopyran, or thiophene; the heterocycles being optionally substituted
5 with halogen or alkyl,

R₃ and R₄ are H, alkyl, halogen, CF₃, CH₃O, CH₃S or NO₂ or R₃ and R₄ with the carbons to which they are attached can form a methylenedioxy group,

R₅ is H, and

10 Z is a heterocycle which can be pyridine, thiazole, benzothiazole, benzimidazole or quinoline, which Z group can optionally be substituted with halogen or alkyl.

The preferred pyridazinone derivative is



15

which may be prepared as disclosed in French Patent No. 2,647,676.

Preferred aP2 inhibitors for use herein will include an oxazole ring.

20 Unless otherwise indicated, the term "lower alkyl", "alkyl" or "alk" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 40 carbons, preferably 1 to 20 carbons, more preferably 1 to 12 carbons, in the normal
25 chain, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethyl-pentyl, nonyl, decyl, undecyl, dodecyl, the various branched chain isomers thereof, and the like as well as such groups including 1 to

4 substituents such as halo, for example F, Br, Cl or I or CF₃, alkoxy, aryl, aryloxy, aryl(aryl) or diaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, hydroxy, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, haloalkyl, trihaloalkyl and/or alkylthio.

Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclicalkyl, bicyclicalkyl and tricyclicalkyl, containing a total of 3 to 20 carbons forming the rings, preferably 4 to 12 carbons, forming the ring and which may be fused to 1 or 2 aromatic rings as described for aryl, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl,

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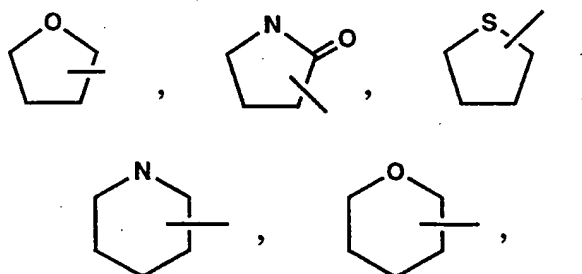
any of which groups may be optionally substituted with 1 to 4 substituents such as halogen, alkyl, alkoxy, hydroxy, aryl, aryloxy, arylalkyl, cycloalkyl, alkylamido, alkanoylamino, oxo, acyl, arylcarbonylamino, amino, nitro, cyano, thiol and/or alkylthio.

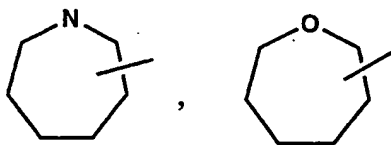
Unless otherwise indicated the term "aryl" or "Ar" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl) and may optionally include one to three additional rings fused to Ar (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings) and may be optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, haloalkyl, alkyl, haloalkyl,

alkoxy, haloalkoxy, alkenyl, trifluoromethyl,
 trifluoromethoxy, alkynyl, cycloalkylalkyl,
 cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl,
 arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy, arylthio,
 5 arylazo, heteroarylalkyl, heteroarylalkenyl,
 heteroarylheteroaryl, heteroaryloxy, hydroxy, nitro, cyano,
 amino, substituted amino wherein the amino includes 1 or 2
 substituents (which are alkyl, aryl or any of the other
 aryl compounds mentioned in the definitions), thiol,
 10 alkylthio, arylthio, heteroarylthio, arylthioalkyl,
 alkoxyarylthio, alkylcarbonyl, arylcarbonyl,
 alkylaminocarbonyl, arylaminocarbonyl, alkoxy carbonyl,
 aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy,
 alkylcarbonylamino, arylcarbonylamino, arylsulfinyl,
 15 arylsulfinylalkyl, arylsulfonylamino or
 arylsulfonaminocarbonyl.

Unless otherwise indicated the term "aralkyl",
 "aryl-alkyl" or "aryllower alkyl" as used herein alone or
 as part of another group refers to alkyl groups as
 20 discussed above having an aryl substituent, such as benzyl
 or phenethyl, or naphthylpropyl, or an aryl as defined
 above.

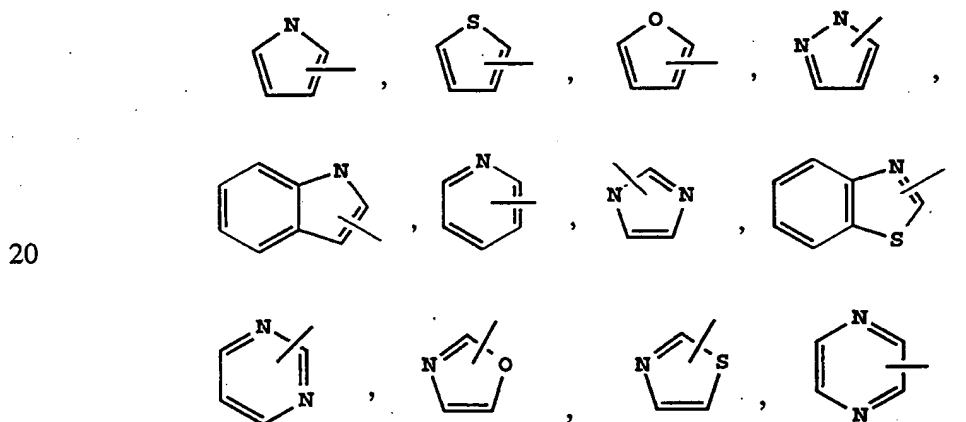
Unless otherwise indicated, the term
 "cycloheteroalkyl" as used herein alone or as part of
 25 another group refers to a 5-, 6- or 7-membered saturated or
 partially unsaturated ring which includes 1 to 2 hetero
 atoms such as nitrogen, oxygen and/or sulfur, linked
 through a carbon atom or a heteroatom, where possible,
 optionally via the linker $(CH_2)_p$ (where p is 1, 2 or 3),
 30 such as





and the like. The above groups may include 1 to 3 substituents such as any of the substituents for alkyl or aryl as defined above. In addition, any of the above rings can be fused to 1 or 2 cycloalkyl, aryl, heteroaryl or cycloheteroalkyl rings.

Unless otherwise indicated, the term "heteroaryl" (also referred to as heteroaryl) as used herein alone or as part of another group refers to a 5- or 6-membered aromatic ring which includes 1, 2, 3 or 4 hetero atoms such as nitrogen, oxygen or sulfur, and such rings fused to an aryl, cycloalkyl, heteroaryl or cycloheteroalkyl ring (e.g. benzothioophenyl, indolyl), linked through a carbon atom or a heteroatom, where possible, optionally via the linker $(CH_2)_p$ (which is defined above), such as



and the like.

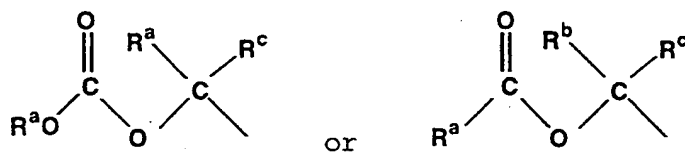
The heteroaryl groups including the above groups may optionally include 1 to 4 substituents such as any of the substituents listed for aryl. In addition, any of the above rings can be fused to a cycloalkyl, aryl, heteroaryl or cycloheteroalkyl ring.

The term "prodrug esters" as employed herein includes prodrug esters which are known in the art for both

phosphorus and carboxylic acids such as similar carboxylic acid esters such as methyl, ethyl benzyl and the like.

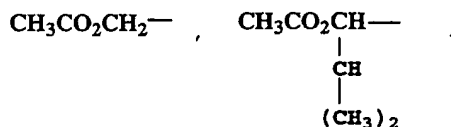
Other examples include the following groups: (1-alkanoyloxy)alkyl such as,

5



wherein R^a , R^b and R^c are H, alkyl, aryl or aryl-alkyl; however R^aO cannot be HO. Examples of such prodrug esters include

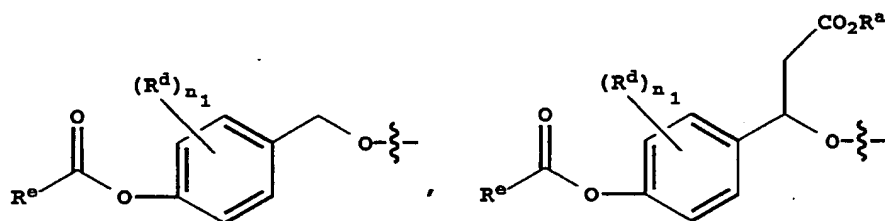
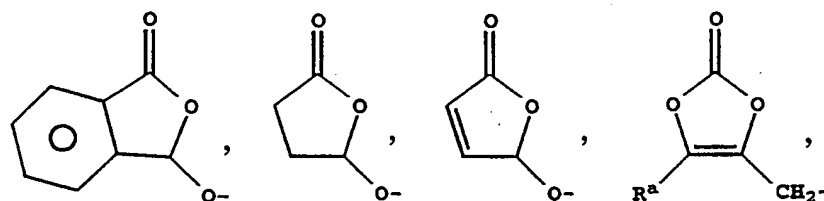
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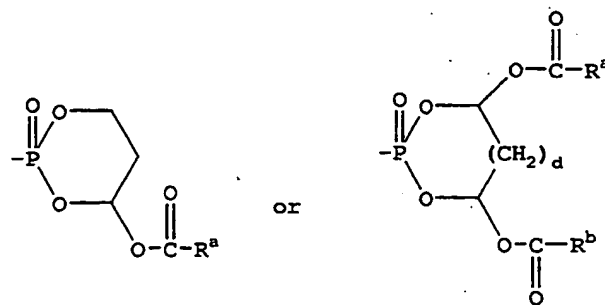
$t\text{-C}_4\text{H}_9\text{CO}_2\text{CH}_2-$, or



15 Other examples of suitable prodrug esters include



20 wherein R^a can be H, alkyl (such as methyl or t -butyl), arylalkyl (such as benzyl) or aryl (such as phenyl); R^d is H, alkyl, halogen or alkoxy, R^e is alkyl, aryl, arylalkyl or alkoxy, and n_1 is 0, 1 or 2; or



(d is 0 to 3)

Where the α P2 inhibitor is in acid form it may form a pharmaceutically acceptable salt such as alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium as well as zinc or aluminum and other cations such as ammonium, choline, diethanolamine, ethylenediamine, t-butylamine, t-octylamine, dehydroabietylamine.

Where desired, the α P2 inhibitor may be used in combination with another antidiabetic agent (also referred to herein as "another antihyperglycemic agent") which may be administered orally in the same dosage form in accordance with the invention, a separate oral dosage form or by injection.

The other antidiabetic agent may be a biguanide, a sulfonyl urea, a glucosidase inhibitor, a thiazolidinedione, an insulin sensitizer, a glucagon-like peptide-1 (GLP-1), insulin or a PPAR α/γ dual agonist and/or a meglitinide.

It is believed that the use of the α P2 inhibitor in combination with another antidiabetic agent produces antihyperglycemic results greater than that possible from each of these medicaments alone and greater than the combined additive anti-hyperglycemic effects produced by these medicaments.

The other antidiabetic agent may be an oral antihyperglycemic agent preferably a biguanide such as metformin or phenformin or salts thereof.

Where the other antidiabetic agent is a biguanide, the α P2 inhibitor will be employed in a weight ratio to biguanide within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 2:1.

5 The other antidiabetic agent may also preferably be a sulfonyl urea such as glyburide (also known as glibenclamide), glimepiride (disclosed in U.S. Patent No. 4,379,785), glipizide, gliclazide or chlorpropamide, other known sulfonylureas or other antihyperglycemic
10 agents which act on the ATP-dependent channel of the β -cells, with glyburide being preferred.

 The α P2 inhibitor will be employed in a weight ratio to the sulfonyl urea in the range from about 0.01:1 to about 100:1, preferably from about 0.2:1 to about
15 10:1.

 The oral antidiabetic agent may also be a glucosidase inhibitor such as acarbose (disclosed in U.S. Patent No. 4,904,769) or miglitol (disclosed in U.S. Patent No. 4,639,436), which may be administered in a
20 separate oral dosage form.

 The α P2 inhibitor will be employed in a weight ratio to the glucosidase inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 50:1.

25 The α P2 inhibitor may be employed in combination with a thiazolidinedione oral antidiabetic agent or other insulin sensitizers (which has an insulin sensitivity effect in NIDDM patients) such as troglitazone (Warner-Labert's Rezulin[®], disclosed in U.S. Patent No.
30 4,572,912), rosiglitazone (SKB), pioglitazone (Takeda), Mitsubishi's MCC-555 (disclosed in U.S. Patent No. 5,594,016), Glaxo-Welcome's GL-262570, englitazone (CP-68722, Pfizer) or darglitazone (CP-86325, Pfizer).

 The α P2 inhibitor will be employed in a weight
35 ratio to the thiazolidinedione in an amount within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 5:1.

The sulfonyl urea and thiazolidinedione in amounts of less than about 150 mg oral antidiabetic agent may be incorporated in a single tablet with the α P2 inhibitor.

The α P2 inhibitor may also be employed in
5 combination with a non-oral antihyperglycemic agent such as insulin or with glucagon-like peptide-1 (GLP-1) such as GLP-1(1-36) amide, GLP-1(7-36) amide, GLP-1(7-37) (as disclosed in U.S. Patent No. 5,614,492 to Habener, the disclosure of which is incorporated herein by reference),
10 which may be administered via injection, or by transdermal or buccal devices.

Where present, metformin, the sulfonyl ureas, such as glyburide, glimepiride, glipyrider, glipizide, chlorpropamide and gliclazide and the glucosidase
15 inhibitors acarbose or miglitol or insulin may be employed in formulations as described above and in amounts and dosing as indicated in the Physician's Desk Reference.

Where present, metformin or salt thereof may be
20 employed in amounts within the range from about 500 to about 2000 mg per day which may be administered in single or divided doses one to four times daily.

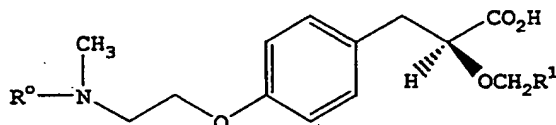
Where present, the thiazolidinedione antidiabetic agent may be employed in amounts within the range from
25 about 0.01 to about 2000 mg/day which may be administered in single or divided doses one to four times per day.

Where present, insulin may be employed in formulations, amounts and dosing as indicated by the Physician's Desk Reference.

30 Where present, GLP-1 peptides may be administered in oral buccal formulations, by nasal administration or parenterally as described in U.S. Patent Nos. 5,346,701 (TheraTech), 5,614,492 and 5,631,224 which are incorporated herein by reference.

35 The α P2 inhibitor may be employed in combination with another antidiabetic agent which may be a PPAR α/γ dual agonist such as an N-benzylthiazolidylbenzamide

derivative such as disclosed in WO 96/38428 such as 5-
 (2,4-dioxothiazolidin-5-ylmethyl)-2-methoxy-N-[4-
 (trifluoromethyl)benzyl]benzamide (KRP-297), WO 98/05531
 (Ligand Pharmaceuticals, Inc.) which discloses 2-(4-[2,4-
 5 difluorophenyl]-1-heptylureido)ethyl]phenoxy)-2-
 methylbutyric acid, and WO 97/25042 and WO96/04260 (SKB)
 which disclose benzoxazole and pyridine derivatives of
 the structure



10 or a pharmaceutically acceptable salt thereof, and/or a
 pharmaceutically acceptable solvate thereof, wherein R⁰
 represents 2-benzoxazolyl or 2-pyridyl and R¹ represents
 CH₂OCH₃ or CF₃, such as (S)-3-[4-[2-[N-(2-benzoxazolyl)-N-
 methylamino]ethoxy]phenyl]-2-(2-methoxy-ethoxy)propanoic
 15 acid; or (S)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]-
 ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoic acid;
 or a pharmaceutically acceptable salt thereof, and/or a
 pharmaceutically acceptable solvate thereof. Dosages
 employed are as set out in the above references.

20 The aP2 inhibitor will be employed in a weight
 ratio to the PPAR α/γ dual agonist within the range from
 about 0.01:1 to about 100:1, preferably from about 0.5:1
 to about 5:1.

Where the aP2 inhibitor is employed in combination
 25 with the PPAR α/γ dual agonist, the combination may be
 employed in an oral dosage form such as a tablet or
 capsule as will be apparent to one skilled in the art.

Where present, the meglitinide, for example,
 repaglinide (Prandin[®], Novartis) or nataglinide (Starlix[®],
 30 Novartis) may be employed in formulations, amounts and
 dosing as indicated in the Physician's Desk Reference.

The aP2 inhibitor will be employed in a weight
 ratio to the meglitinide within the range from about
 0.01:1 to about 100:1, preferably from about 0.5:1 to
 35 about 50:1.

In carrying out the method of the invention, a pharmaceutical composition will be employed containing at least one aP2 inhibitor with or without another antidiabetic agent in association with a pharmaceutical vehicle or diluent. The pharmaceutical composition can be formulated employing conventional solid or liquid vehicles or diluents and pharmaceutical additives of a type appropriate to the mode of desired administration. The compounds can be administered to mammalian species including humans, monkeys, dogs, etc. by an oral route, for example, in the form of tablets, capsules, granules or powders, or they can be administered by a parenteral route in the form of injectable preparations. The dose for adults is preferably between 50 and 2,000 mg per day, which can be administered in a single dose or in the form of individual doses from 1-4 times per day.

A typical capsule for oral administration contains aP2 inhibitor (250 mg), lactose (75 mg) and magnesium stearate (15 mg). The mixture is passed through a 60 mesh sieve and packed into a No. 1 gelatin capsule.

A typical injectable preparation is produced by aseptically placing 250 mg of aP2 inhibitor into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 mL of physiological saline, to produce an injectable preparation.

Compounds sufficiently satisfying the structural criteria described above may be determined by use of an in vitro assay system which measures the potentiation of inhibition of aP2 by displacement of a fluorescent substrate from aP2 by the inhibitor. Inhibition constants (K_i values) for the inhibitors may be determined by the method described below:

Production of purified recombinant human aP2 protein. Recombinant human aP2 protein is produced by

standard recombinant DNA technology. In the typical case, aP2 is produced by heterologous expression in *E. coli* strain BL21(D53) transformed with pET11a vector containing the full length human aP2 cDNA (Baxa, C.A., Sha, R.S., Buelte, M.K., Smith, A.J., Matarese, V., Chinander, L.L., Boundy, K.L., and Bernlohr, D.A. (1989). Human adipocyte lipid-binding protein: purification of the protein and cloning of its complementary DNA. *Biochemistry* 28: 8683-8690 and Xu, Z., Buelte, M.K., Banaszak, L.J., and Bernlohr, D.A. (1991). Expression, purification and crystallization of the adipocyte lipid binding protein. *J. Biol. Chem.* 266: 14367-14370). Purification of aP2 from *E. coli* is conducted as described by Xu, yielding essentially homogeneous aP2 protein with molecular weight ~14600 daltons and free of endogenous fatty acids. The purified aP2 is capable of binding up to one mole of free fatty acid per mole protein. The binding and structural properties of recombinant aP2 protein were previously shown to be identical to aP2 protein isolated from adipose tissue.

20

In vitro assay of aP2 inhibitors. Inhibitors of aP2 are evaluated in a homogeneous fluorescent-based competition assay using recombinant aP2 protein and 1,8-anilino-naphthalene-sulfonic acid (1,8-ANS) as assay substrate. This competition assay was adapted from generalized procedures described previously (Kane, C.D. and Bernlohr, D.A. (1996). A simple assay for intracellular lipid-binding proteins using displacement of 1-anilino-8-sulfonic acid. (1996) *Anal. Biochem.* 233: 197-204 and Kurian E., Kirk, W.R. and Prendergast, F.G. (1996) Affinity of fatty acid for r-rat intestinal fatty acid binding protein. *Biochemistry*, 35, 3865-3874). The method relies on the increase in fluorescence quantum yield of 1,8-ANS upon binding to the fatty acid binding site of aP2. The assay is run using appropriate concentrations of inhibitor, 1,8-ANS, and aP2 protein, in order to calculate the inhibitor binding constant (K_i) for compounds being

evaluated. The K_i calculation was based on the procedure previously described for calculation of dissociation constants described by Kurian. Lower K_i values indicate higher affinities of compounds binding to aP2.

5 In the assay as conducted for the inhibitors described herein, a series of aliquots of aP2 (5 μ M) in solution in 10 mM potassium phosphate buffer (pH 7.0) are mixed with an equimolar concentration of test compound, followed by the addition of a series of increasing
10 concentrations of 1,8-ANS (from 0 to 5 μ M). The assay typically is conducted in 96-well plate format with reagents added using robotic instrumentation (Packard Multiprobe 104). The fluorescence value for each test is determined using a Cytofluor-4000 multi-well fluorescence
15 plate reader (Perceptive Biosystems) using excitation wavelength 360 nm and emission wavelength 460 nm, or using other suitable spectrofluorometer. In preparation for the assay, test compounds are initially prepared at 10 mM in dimethylsulfoxide. All subsequent dilutions and assay
20 additions are made in 10 mM potassium phosphate buffer, pH 7.0.

X-ray crystallography of the inhibitor-aP2 complex can be performed by one skilled in the art using contemporary biophysical methodologies and commercial
25 instrumentation. Such crystallographic data can be used to conclusively determine if a compound used in the present invention has embodied the structural requirement necessary for inhibition of aP2. An example of such an X-ray crystallographic determination is presented below:

30 Crystals of aP2 complexed with the inhibitors were typically grown by the hanging drop method. aP2, at 8.3 mg/ml, was pre-equilibrated with 1-5 mM of the inhibitor in 0.1 M Tris-HCl pH 8.0, 1% w/v DMSO for four hours. 2 μ l drops containing equilibrated protein and reservoir
35 solution at a 1:1 ratio were suspended on plastic cover slips and equilibrated against a 1 ml reservoir containing 2.6-3.0 M ammonium sulfate in 0.1 M Tris-HCl pH 8.0.

Crystals typically appeared in 2-3 days and reached maximum size within 2 weeks. Data was typically collected on a single flash-frozen crystal (Oxford Cryosystems) using a Rigaku rotating anode and an R-axis II image plate detector of a Bruker multiwire area detector. Diffraction from ap2 crystals was excellent. Diffraction was consistently observed to better than 2.0 Å resolution often to beyond 1.5 Å resolution. Data was processed either with DENZO/SCALEPACK (R-axis II data), or Xengen (Bruker data). XPLOR was used for structure refinement and model building was done using the molecular modeling package CHAIN. After a single round of refinement, examination of the $F_o - F_c$ map typically allowed facile building of the inhibitor into ap2 binding cavity. Iterative fitting and refinement were continued until improvement was no longer seen in the electron density map or R-free.

Referring to the accompanying Figure which is a computer generated image of a partial X-ray structure of compound XVIA bound to human ap2, the ball and stick figure in light gray is compound XVIA. The Arg106, Arg126, and Tyr128 residues are depicted as ball and stick figures in dark gray. The dark spheres represent a space filling view of the discrete binding pocket comprised of the residues Phe16, Tyr19, Met20, Val23, Val25, Ala33, Phe57, Thr74, Ala75, Asp76, Arg78. The 4-chlorophenyl substituent of compound XVIA is shown bound within this discrete pocket and the hydroxyl group is bound to the Arg-Tyr-Arg residues.

What is claimed is:

1. A method for treating diabetes, insulin resistance, obesity, hyperglycemia, hyperinsulinemia, or elevated fatty acids, or glycerol, or hypertriglyceridemia
5 which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of an aP2 inhibitor.
2. The method as defined in Claim 1 wherein the aP2 inhibitor binds to the aP2 protein and inhibits its
10 function and/or its ability to bind free fatty acids.
3. The method as defined in Claim 1 wherein the aP2 inhibitor contains a hydrogen bond donator or acceptor group and interacts directly or through an intervening water molecule either by ionic or hydrogen bonding
15 interactions, with one, two, or three of the three amino acid residues, designated as Arg 106, Arg 126 and Tyr 128 in human aP2 within the aP2 protein.
4. The method as defined in Claim 3 wherein the hydrogen bond donator or acceptor group is acid in nature.
- 20 5. The method as defined in Claim 3 where said aP2 inhibitor contains an additional substituent which binds to (in) and/or interacts with a discrete pocket within the aP2 protein defined roughly by the amino acid residues Phe 16, Tyr 19, Met 20, Val 23, Val 25, Ala 33, Phe 57, Thr 74, Ala
25 75, Asp 76, Arg 78 in human aP2.
6. The method as defined in Claim 5 wherein said additional substituent in said aP2 inhibitor is hydrophobic in nature.
7. The method as defined in Claim 5 in which the
30 through space distance from the hydrogen bond donor/acceptor group and the additional substituent group in said aP2 inhibitor is within the distance of about 7 to about 15 Angstroms.
8. The method as defined in Claim 1 wherein Type II
35 diabetes is treated.

9. The method as defined in Claim 1 wherein the aP2 inhibitor is employed in the form of a pharmaceutically acceptable salt thereof or a prodrug ester thereof.

10. The method as defined in Claim 1 wherein the aP2 inhibitor includes an oxazole or analogous ring, a pyrimidine derivative or a pyridazinone derivative.

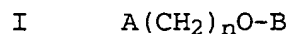
11. The method as defined in Claim 10 wherein the aP2 inhibitor is a substituted benzoyl or biphenyl-2-oxazole-alkanoic acid derivative, an oxazole derivative, a 2-thio-4,5-diphenyloxazole S-derivative, a phenyl-heterocyclic oxazole derivative, a diaryloxazole derivative, a 4,5-diphenyloxazole derivative, an oxazole carboxylic acid derivative, a phenyloxazolyloxazole derivative, or a 2-(4,5-diaryl)-2-oxazolyl substituted phenoxyalkanoic acid derivative.

12. The method as defined in Claim 10 wherein the aP2 inhibitor is a 2-benzyloxypyrimidine derivative, a dihydro(alkylthio)(naphthylmethyl)oxypyrimidine derivative, a thiouracil derivative, or an α -substituted pyrimidine-thioalkyl or alkyl ether derivative.

13. The method as defined in Claim 10 wherein the aP2 inhibitor is a pyridazinone acetic acid derivative.

14. The method as defined in Claim 10 wherein the aP2 inhibitor is

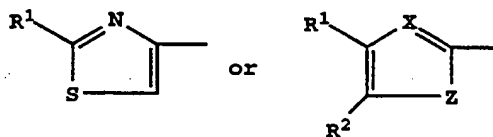
(I) a substituted benzoylbenzene or biphenyl alkanoic acid derivative having the structure:



wherein

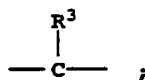
A is a group having the formula

30

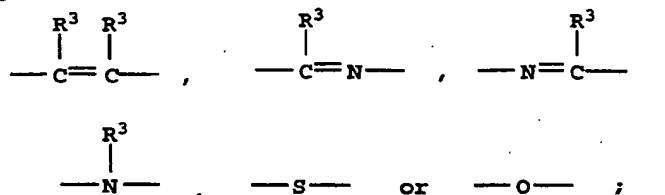


wherein

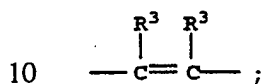
X is -N- or



Z is



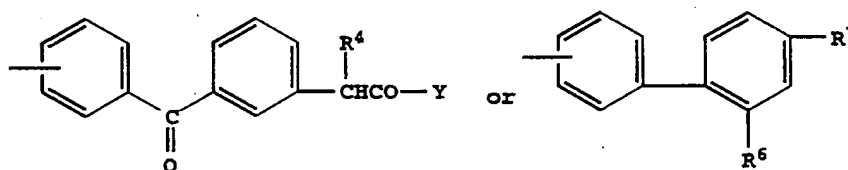
- 5 R^1 is hydrogen, lower alkyl or phenyl;
 R^2 is hydrogen or lower alkyl; or
 R^1 and R^2 taken together form a benzene ring, with
the proviso that when X is -N-, Z is other than



R^3 is hydrogen or lower alkyl;

n is 1-2;

B is



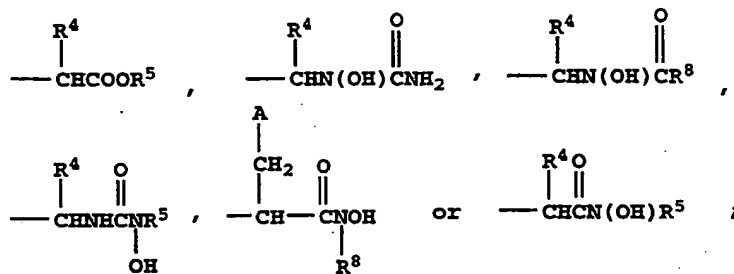
15 wherein

Y is OR^5 or N(OH)R^8 ;

R^4 and R^5 are each, independently, hydrogen or lower
alkyl;

R^6 is hydrogen, halo or nitro;

20 R^7 is



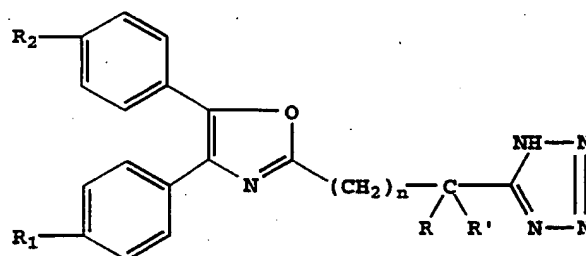
R^8 is lower alkyl;

m is 0-3;

25 or a pharmacologically acceptable salts thereof;

(II) oxazole derivatives which have the structure

II



in which;

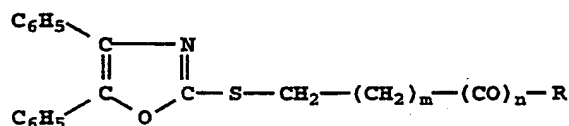
R and R' are identical or different and represent a
5 hydrogen atom or an alkyl radical containing 1 or 2 carbon
atoms,

R₁ and R₂ are identical or different and represent
hydrogen or halogen atoms or alkyloxy radicals in which the
alkyl portion contains 1 to 4 carbon atoms in a straight or
10 branched chain, and

n equals 3 to 6, as well to their salts;

(III) 2-thiol-4,5-diphenyloxazole S-derivatives
which have the structure

III



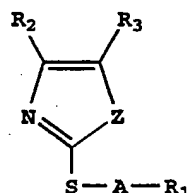
15

wherein m is 0, 1 or 2, n is 1 and R represents hydroxy,
alkoxy or amino, and pharmaceutically acceptable addition
salts thereof;

(IV)azole derivatives of the structure

20

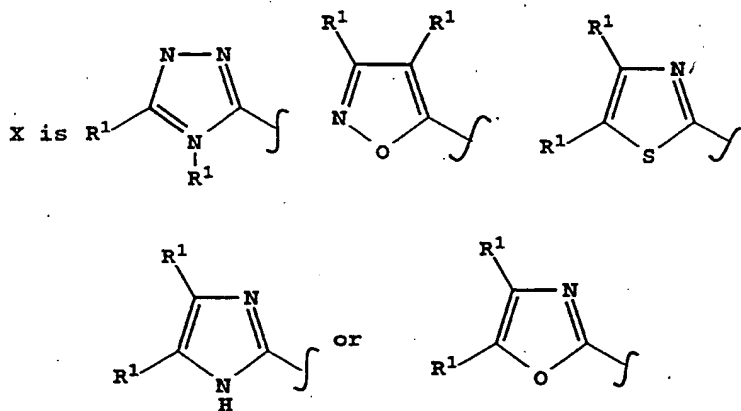
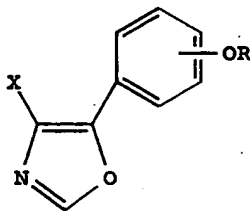
IV



wherein R₁ is carboxyl, esterified carboxyl or other
functionally modified carboxyl group; R₂ and R₃ each are
aryl of up to 10 carbon atoms; A is C_nH_{2n} in which n is an
25 integer from 1 to 10, inclusive; and Z is O or S, and
physiologically acceptable salts thereof;

(V) phenyl-heterocyclic oxazole derivatives which have the structure

V

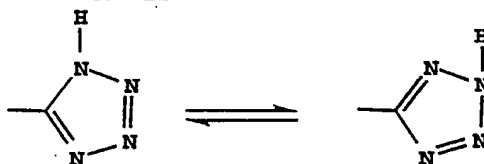


5

R is CH_2R^2 ;

R^1 is Ph or Th;

R^2 is



CO_2R^3 ; and

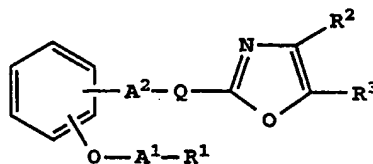
10

R^3 is H, or C_1 - C_4 lower alkyl;

or pharmaceutically acceptable salt thereof;

(VI) diaryloxazole derivatives having the structure

VI



15 wherein R^1 is carboxy or protected carboxy,

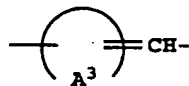
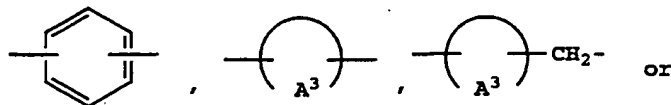
R^2 is aryl,

R^3 is aryl,

A^1 is lower alkylene,

A² is bond or lower alkylene and

-Q- is

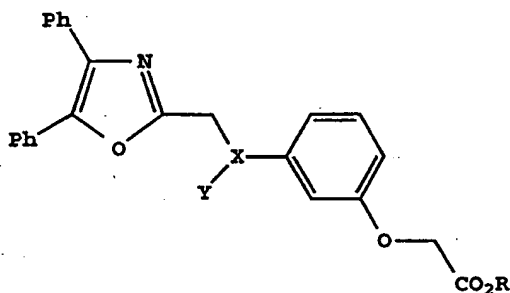


(in which is cyclo (lower)alkane or cycle(lower)alkene,

each of which may have suitable substituent(s));

(VII) 4,5-diphenyloxazole derivatives having the structure

VIIA



10

wherein

R is H or C₁-C₅ lower alkyl,

X is N or CH,

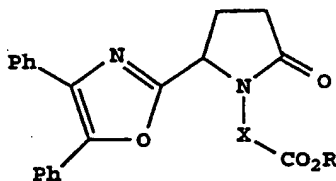
Y is H or CO₂R¹, or COR², provided that when X is CH,

15 Y is not H,

R¹ is C₁-C₅ lower alkyl, or phenylmethyl, and

R² is C₁-C₅ alkyl;

VIIB



20 wherein

R is H or C₁-C₅ lower alkyl,

X is $(CH_2)_n$ or para or meta substituted phenyl

wherein the substituent is OR^2 ,

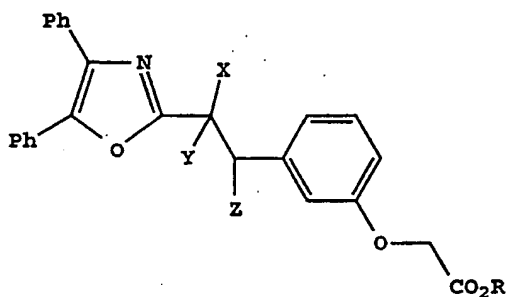
R^2 is C_1 - C_5 alkyl, and

n is an integer of 4 to 8,

5 and pharmaceutically acceptable salts thereof;

(VIII) oxazole carboxylic acid derivatives having the structure

VIII



10

wherein

Y and Z are independently hydrogen or together form a bond;

X is CN, CO_2R^1 or $CONR^2R^3$;

15

R and R^1 are independently or together H, Na, or C_1 - C_5 lower alkyl;

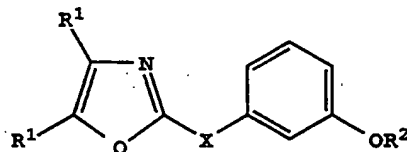
R^2 and R^3 are independently or together H, or C_1 - C_5 lower alkyl;

or alkali metal salt thereof;

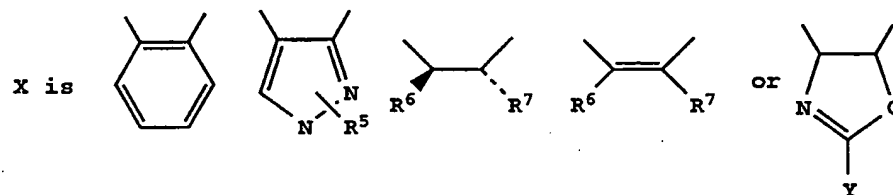
20

(IX) phenyloxazolyloxazole derivatives having the structure

IX

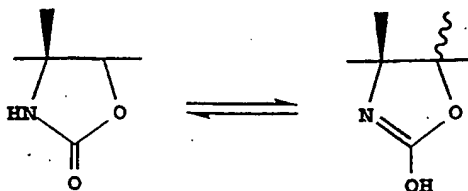


wherein



25

Y is CH₃, Ph, or OH, provided that when Y is OH, the compound exists in the keto-enol tautomerism form



R¹ is Ph or Th;

5 R² is CH₂R³;

R³ is CO₂R⁴;

R⁴ is H or C₁-C₅ lower alkyl;

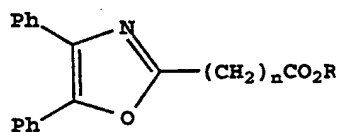
R⁵ is H or CH₃; R⁶ is OHCHN or H₂N; and

R⁷ is H or OH;

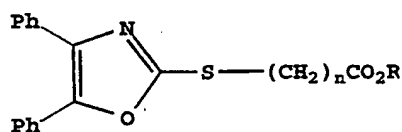
10 or pharmaceutically acceptable salt thereof;

(X) 2-(4,5-diaryl)-2-oxazolyl substituted phenoxyalkanoic acids and esters having the structure

XA

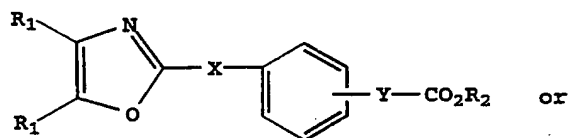


15 XB



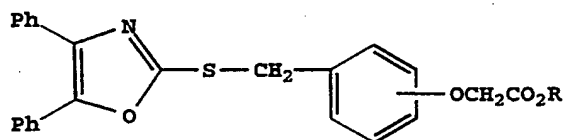
(wherein n is 7-9 and R is hydrogen or lower alkyl; or when R is hydrogen, the alkali metal salt thereof),

XC



20

XD



wherein

R₁ is phenyl or thienyl;

R_2 is hydrogen, lower alkyl or together with CO_2 is tetrazol-1-yl;

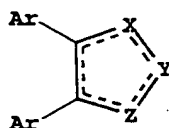
X is a divalent connecting group selected from the group consisting of CH_2CH_2 , $CH=CH$, and CH_2O ;

5 Y is a divalent connecting group attached to the 3- or 4-phenyl position selected from the group consisting of OCH_2 , CH_2CH_2 and $CH=CH$,

or when R_2 is hydrogen, an alkali metal salt thereof;

(XI) substituted 4,5-diaryl heterocycles having the
10 formula

XI



in which

each group Ar is the same or different and is
15 optionally substituted phenyl or optionally substituted heteroaryl;

X is nitrogen or CR^1 ;

Y is nitrogen, $N(CH_2)_nA$ or $C(CH_2)_nA$;

Z is nitrogen, oxygen or $N(CH_2)_nA$, and the dotted
20 line indicates the optional presence of a double bond so as to form a fully unsaturated heterocyclic ring;

R^1 is hydrogen, C_{1-4} alkyl, optionally substituted phenyl or optionally substituted heteroaryl;

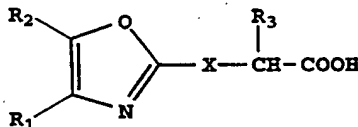
n is 4 to 12; and

25 A is CO_2H or a group hydrolysable to CO_2H , 5-tetrazolyl, SO_3H , $P(O)(OR)_2$, $P(O)(OH)_2$, or $P(O)(R)(OR)$ in which R is hydrogen or C_{1-4} alkyl, or a pharmaceutically acceptable salt thereof;

(XII) compounds which have the structure

30

XII



Where X is O or S;

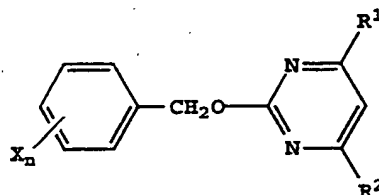
R_1 is H, phenyl or phenyl substituted with F, Cl or Br or alkoxy,

R_2 is H, alkyl, phenyl or phenyl substituted with F, Cl or Br or alkoxy, and

5 R_3 is H or alkyl;

(XIII) 2-benzyloxypyrimidine derivatives having the following structure

XIII



10 wherein

R^1 and R^2 are each independently H, a halogen, hydroxyl, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_3 - C_5 alkenyl, C_3 - C_5 alkynyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, C_3 - C_5 alkenyloxy, C_3 - C_5 alkynyloxy, C_1 - C_4 alkylthio, or phenyl, with the

15 proviso that at least one of R^1 and R^2 must be hydroxyl;

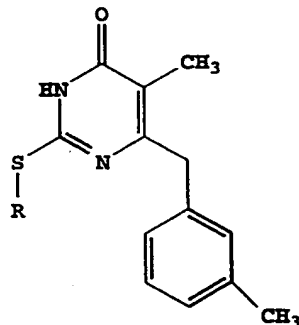
n is an integer of 0 to 5; and

each X which may be identical or different if n is greater than 1, is a halogen, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 alkylthio, C_7 - C_9 aralkyloxy, phenyl,

20 hydroxymethyl, hydroxycarbonyl, C_1 - C_4 alkoxycarbonyl, or nitro;

(XIV) dihydro(alkylthio)-(naphthylmethyl)-oxypyrimidines which have the structures

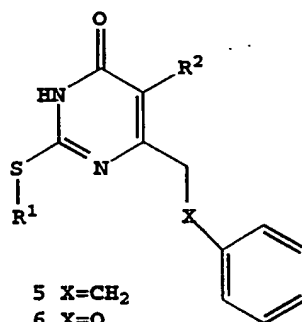
XIVA



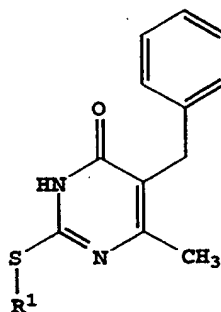
3a R=sec-butyl
3b R=cyclopentyl
3c R=cyclohexyl

25

XIVB

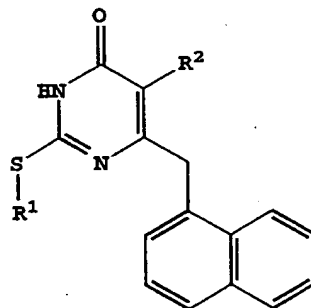


XIVC

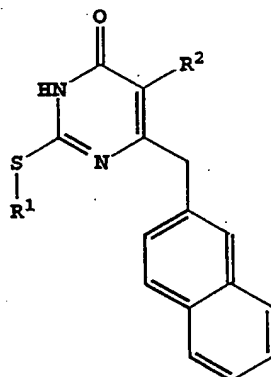


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XIVD



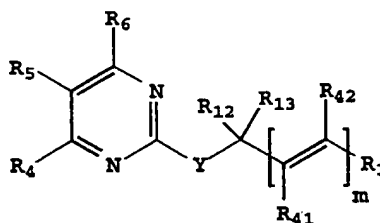
XIVE



- R¹ = sec-butyl, cyclopentyl, cyclohexyl;
10 R² = H, CH₃, including tautomers of the above;

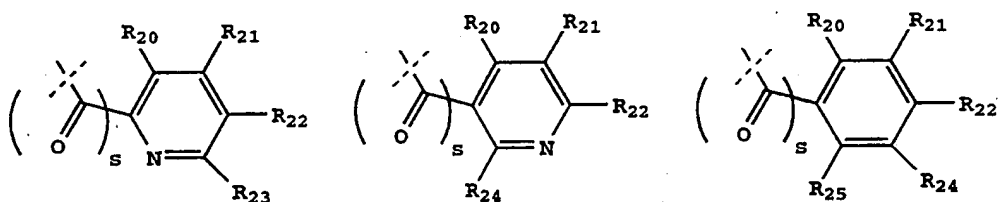
(XVI) α -substituted pyrimidine-thioalkyl and
alkylether compounds which have the structure

XVI



5 where m is 0 or 1;

R¹ is selected from -CO₂R₅₃, -CONR₅₄R₅₅,



10 where s is 0 or 1, and R₂₀, R₂₁, R₂₂, R₂₃, R₂₄, and R₂₅ are
the same or different and are selected from -H, C₁-C₆
alkyl, C₁-C₆ alkenyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₃-C₈
cycloalkyl, -CF₃, -NO₂, -halo, -OH, -CN, phenyl,
phenylthio, -styryl, -CO₂(R₃₁), -CON(R₃₁)(R₃₂), -CO(R₃₁), -
(CH₂)_n-N(R₃₁)(R₃₂), -C(OH)(R₃₁)(R₃₃), -(CH₂)_nN(R₃₁)(CO(R₃₃)),
15 (CH₂)_nN(R₃₁)(SO₂(R₃₃)), or where R₂₀ and R₂₁, or R₂₁ and R₂₂,
or R₂₂ and R₂₃ are taken together to form a five or six-
membered saturated or unsaturated ring containing 0 or 1
oxygen, nitrogen or sulfur, where the unsaturated ring may
be optionally substituted with 1, 2 or 3, C₁-C₆ alkyl, C₁-
20 C₆ alkoxy, -OH, -CH₂OH, -(CH₂)_n-N(R₃₁)(R₃₂), -C₃-C₈
cycloalkyl, -CF₃, -halo, CO₂(R₃₁), -CON(R₃₁)(R₃₂), -CO(R₃₁),
-(CH₂)_nN(R₃₁)(CO(R₃₃)), -(CH₂)_nN(R₃₁)(SO₂(R₃₃)), -CN, -CH₂CF₃
or -CH(CF₃)₂, or phenyl and the saturated ring may be
optionally substituted with 1, 2 or 3, -C₁-C₆ alkyl, -C₁-C₆
25 alkoxy, -OH, -CH₂OH or -(CH₂)_n-N(R₃₁)(R₃₂) or one oxo (=O);
where n is 0-3 and R₃₁, R₃₂ and R₃₃ are the same or
different and are selected from

-H,
C₁-C₆ alkyl,

phenyl optionally substituted with 1, 2 or 3 -halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, -CF₃, -OH or -CN,

or where R₃₁ and R₃₂ taken together with the attached nitrogen to form a ring selected from -pyrrolidinyl, -
5 piperidinyl, -4-morpholinyl, -4-thiomorpholinyl, -4-piperazinyl, -4-(1-C₁-C₆alkyl)piperazinyl, or a member selected from

1-cyclohexenyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-imidazolyl, 4-imidazolyl, 2-benzothiazolyl,
10 2-benzoxazolyl, 2-benzimidazolyl, 2-oxazolyl, 4-oxazolyl, 2-thiazolyl, 3-isoxazolyl, 5-isoxazolyl, 5-methyl-3-isoxazolyl, 5-phenyl-3-isoxazolyl, 4-thiazolyl, 3-methyl-2-pyrazinyl, 5-methyl-2-pyrazinyl, 6-methyl-2-pyrazinyl, 5-chloro-2-thienyl, 3-furyl, benzofuran-2-yl, benzothien-2-
15 yl, 2H-1-benzopyran-3-yl, 2,3-dihydrobenzopyran-5-yl, 1-methylimidazol-2-yl, quinoxalin-2-yl, piperon-5-yl, 4,7-dichlorobenzoxazol-2-yl, 4,6-dimethylpyrimidin-2-yl, 4-methylpyrimidin-2-yl, 2,4-dimethylpyrimidin-6-yl, 2-methylpyrimidin-4-yl, 4-methylpyrimidin-6-yl, 6-
20 chloropiperon-5-yl, 5-chloroimidazol[1,2-a]pyridin-2-yl, 1-H-inden-3-yl, 1-H-2-methyl-inden-2-yl, 3,4-dihydronaphth-1-yl, S-4-isopropenylcyclohexen-1-yl or 4-dihydronaphth-2-yl;

where R₅₃ is selected from -H, C₁-C₆alkyl, C₃-C₆cycloalkyl, phenyl (optionally substituted with 1, 2, or
25 3 -halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, -CF₃, -OH, -CN), or a five or six-membered unsaturated ring containing 0 or 1 oxygen, nitrogen or sulfur, where the unsaturated ring may be optionally substituted with -H, C₁-C₆ alkyl, C₁-C₆ alkoxy, -OH, -CH₂OH, or -(CH₂)_n-N(R₃₁)(R₃₂);

30 where R₅₄ and R₅₅ being the same or different are selected from -H, C₁-C₆ alkyl, allyl, or phenyl (optionally substituted with 1, 2 or 3 -halo, C₁-C₆ alkyl, C₁-C₆ alkoxy or -CF₃), or taken together with the attached nitrogen to form a ring selected from -pyrrolidinyl, -piperidinyl, -4-morpholinyl, -4-thiomorpholinyl, -4-piperazinyl, -4-(1-C₁-
35 C₆alkyl)piperazinyl;

R₄₁ and R₄₂, being the same or different, are selected from -H and C₁-C₄ alkyl;

R₁₂ is selected from -H, C₁-C₆ alkyl, -C₃-C₆ cycloalkyl, -CN, -C(O)NH₂, -C(O)N(C₁-C₆alkyl)(C₁-C₆alkyl), -
5 CO₂H, -CO₂(C₁-C₆alkyl), -CH₂OH, -CH₂NH₂ or -CF₃;

R₁₃ is selected from -H, C₁-C₆ alkyl or -CF₃;

Y is selected from -S-, -S(O)-, -S(O)₂, or -O-;

R₄ is -OH;

R₅ is selected -H, -C₂H₄OH, -C₂H₄-O-TBDMS, halo, -C₃-
10 C₆ cycloalkyl, C₁-C₃ alkoxy, -CH₂CH₂Cl or C₁-C₄ alkyl, with the proviso that R₅ is not isobutyl;

or, when R₆ is hydroxyl, R₄ and R₅ are taken together to form a five or six-membered saturated or unsaturated ring which together with the pyrimidine ring form the group
15 consisting of 7H-pyrrolo[2,3-d]pyrimidine, 5,6-dihydro-7H-pyrrolo[2,3-d]pyrimidine, furo[2,3-d]pyrimidine, 5,6-dihydro-furo[2,3-d]pyrimidine, thieno[2,3-d]pyrimidine, 5,6-dihydro-thieno[2,3-d]pyrimidine, 1H-pyrazolo[3,4-d]pyrimidine, 1H-purine, pyrimido[4,5-d]pyrimidine,
20 pteridine, pyrido[2,3-d]pyrimidine, or quinazoline, where the unsaturated ring may be optionally substituted with 1, 2 or 3, C₁-C₆ alkyl C₁-C₆ alkoxy, -OH, -CH₂OH, or -(CH₂)_n-N(R₃₁)(R₃₂), -C₃-C₈ cycloalkyl, -CF₃, -halo, -CO₂(R₃₁), -CON(R₃₁)(R₃₂), -CO(R₃₁), -(CH₂)_nN(R₃₁)(CO(R₃₃)), -
25 (CH₂)_nN(R₃₁)(SO₂(R₃₃)), and the saturated ring may be optionally substituted with 1, 2 or 3, -C₁-C₆ alkyl, C₁-C₆ alkoxy, -OH, -CH₂OH, or -(CH₂)_n-N(R₃₁)(R₃₂) or one oxo (=O);
and

R₆ is selected from -H, -OH, halo, -CN, -CF₃, -
30 CO₂(R₆₁), -C(O)R₆₁ or -C(O)N(R₆₁)(R₆₂) where R₆₁ and R₆₂ are the same or different and are selected from

-H,

C₁-C₆ alkyl,

phenyl optionally substituted with 1, 2 or 3 -halo,

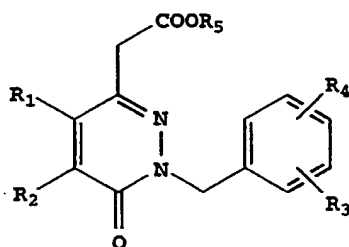
35 C₁-C₆ alkyl, C₁-C₆ alkoxy, -CF₃, -OH, -CN,

or where R₆₁ and R₆₂ taken together with the attached nitrogen to form a ring selected from -pyrrolidinyl, -

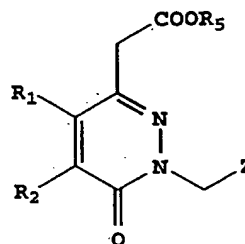
piperidinyl, -4-morpholinyl, -4-thiomorpholinyl, -4-piperazinyl, or -4-(C₁-C₆ alkyl)piperazinyl;

pharmaceutically acceptable salts, hydrates, N-oxides and solvates thereof;

5 (XVII) compounds which have the structure



XVIIA



XVIIIB

where R₁ and R₂ are H, alkyl, aryl or arylalkyl, where the alkyl can include as substituents halogen, CF₃, CH₃O, CH₃S, NO₂, or R₁ and R₂ with the carbons to which they are attached can form methylenedioxy, or

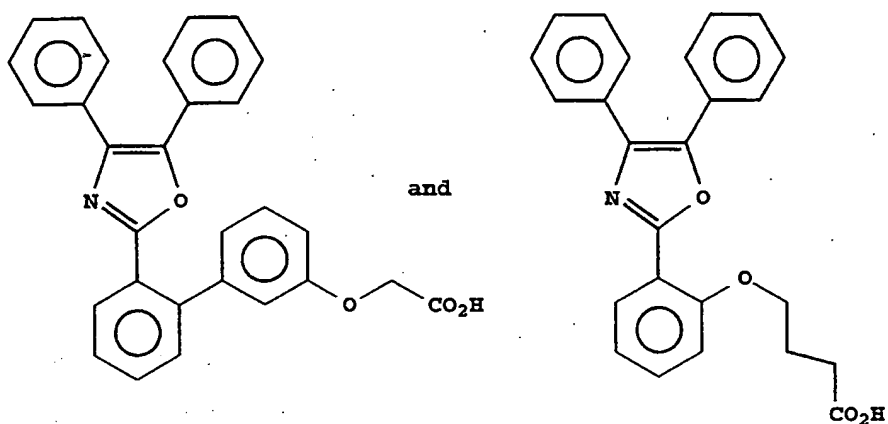
R₁ and R₂ can form a C₃-C₇ non-aromatic ring, or a heterocycle which can be pyridine, pyrazine, pyrimidine, pyridazine, indol, or pyrazole, or an oxygen containing heterocycle which can be pyran or furan, or a sulfur containing heterocycle which can be thiopyran, or thiophene; the heterocycles being optionally substituted with halogen or alkyl,

R₃ and R₄ are H, alkyl, halogen, CF₃, CH₃O, CH₃S or NO₂ or R₃ and R₄ with the carbons to which they are attached can form a methylenedioxy group,

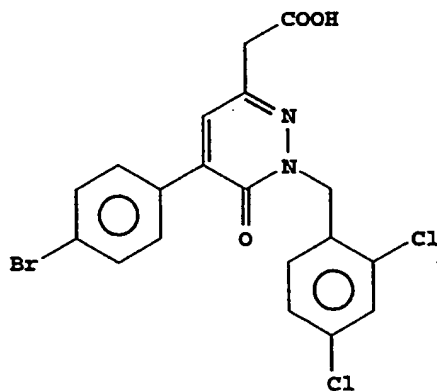
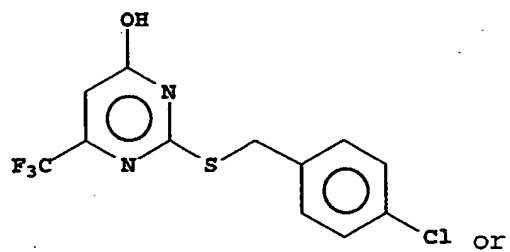
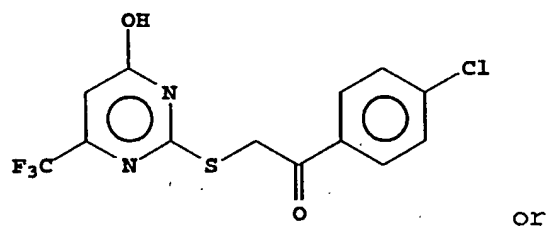
R₅ is H, and

Z is a heterocycle which can be pyridine, thiazole, benzothiazole, benzimidazole or quinoline, which Z group can optionally be substituted with halogen or alkyl.

15. The method as defined in Claim 1 wherein the aP2 inhibitor has the structure



5



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16. A pharmaceutical combination comprising an aP2 inhibitor and another type antidiabetic agent.

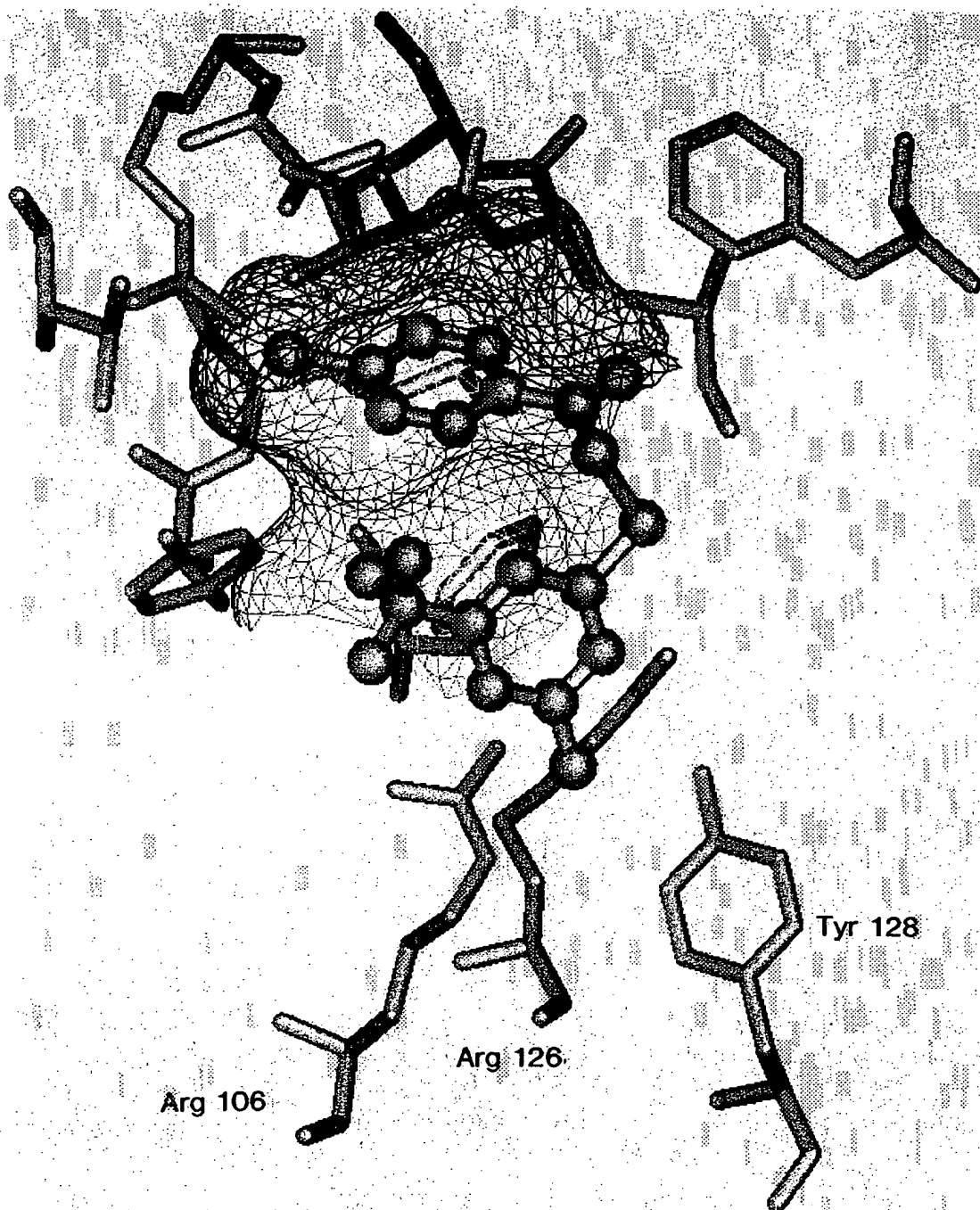
17. The combination as defined in Claim 16 wherein
5 the antidiabetic agent is a biguanide, a sulfonyl urea, a glucosidase inhibitor, a thiazolidinedione, an insulin sensitizer, a glucagon-like peptide-1 (GLP-1), insulin, a PPAR α/γ dual agonist and/or a meglitinide.

18. The combination as defined in Claim 16 wherein
10 the antidiabetic agent is metformin, glyburide, glimepiride, glipyrice, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, troglitazone, insulin, KRP-297, repaglinide and/or nataglinide.

19. The combination as defined in Claim 16 wherein
15 the aP2 inhibitor is present in a weight ratio to the antidiabetic agent within the range from about 0.01 to about 100:1.

20. A method for treating insulin resistance, diabetes, obesity, hyperglycemia, hyperinsulinemia, or
20 elevated blood levels of free fatty acids, or glycerol, or hypertriglyceridemia, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a pharmaceutical combination as defined in Claim 16.

25



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/20946

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/50, 31/505, 31/42

US CL : 514/247, 274, 374, 866

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/247, 274, 374, 866

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE: ap2 inhibitor, albp, adipocyte lipid binding protein with diabet?, insulin?, obes?, glycem?, triglycerid?

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chem. abstr., Vol. 126, 1996 (Columbus, OH, USA), the abstract No. 17417, HOTMISLIGIL, G.S. et al. 'Uncoupling of Obesity From Insulin Resistance Through a Targeted Mutation in aP2, The Adipocyte Fatty Acid Binding Protein.' Science (Washington, D.C.) 1996, 274(5291), 1377-1379.	1-20
A	US 5,218,124 A (FAILLI et al) 08 June 1993.	1-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

14 JANUARY 2000

Date of mailing of the international search report

10 FEB 2000

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